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LYON & LYON LLP
633 WEST FIFTH STREET
SUITE 4700
LOS ANGELES, CA 90071

EXAMINER	
TAYLOR, JANELL E	

ART UNIT	PAPER NUMBER
1634	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/865,807	Applicant(s) CARRINO ET AL.	
	Examiner Janell Cleveland Taylor	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-210* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-210* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 71 and 169 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the restriction endonuclease "BstBNI" is not found in the art, and is not properly defined by the claims. For purposes of examination, it is assumed this is a typographic error and "BstNI" is assumed. It is noted that "BstNBI" is also in the specification, so it is requested which is meant in this particular case.

3. Claims 66 and 154 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims contain the phrase "electronically denaturing." It is not clear what is meant by this phrase. Furthermore, no further explanation is given as to how nucleic acids may be "electronically denatured." Appropriate clarification or correction is required.

4. Claim 134 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim contains the phrase "electronically washing." It is not clear what is meant by this phrase. Furthermore, no further explanation is given as

to how nucleic acids may be "electronically washed." Appropriate clarification or correction is required.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 44-210 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of U.S. Patent No. 6,238,868 in view of Walker et al. (Proc. Nat'l Acad. Sci., 1992, Vol. 89, pages 392-396. Carrino et al. ('868) teach a method for the amplification of one or more target nucleic acid sequences of interest comprising : a) contacting first and second oligonucleotide ligation probes to adjacent nucleic acid sequences of any one of said target sequences such that a 3' terminus of one of said probes is juxtaposed to a 5' terminus of the other of said probes while both the first and second probes are in contact with said target sequence, b) ligating together said oligonucleotide probes at their respective juxtaposed termini to form a ligated target probe template; c) using said ligated target probe

template in a strand displacement amplification reaction to form amplicons of said ligated target probe template wherein no bumper primers are used in said strand displacement amplification.

Carrino does not teach an amplification primer which binds to the target probe and contains a recognition sequence.

Walker teaches the basis for strand displacement amplification (SDA). He teaches that a fundamental reaction scheme of SDA includes a single-stranded target DNA fragment which binds to an SDA primer which contains a recognition sequence. (Fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Carrino and Walker. This is because Walker teaches the basis for SDA, and included in the standard use of SDA is a primer containing a restriction site. Furthermore, using a restriction site would have allowed for the restriction endonuclease to nick the unprotected primer strand and of the recognition site, leaving intact the complementary strand. This would have allowed for the continuous production of single-stranded complements of the target nucleic acid.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

8. Claims 44-45, 56, 58-59, 61-66 and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by You et al. (USPN 5,747,259).

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55). Therefore, You et al. anticipates the claims because it teaches two adjacent oligonucleotides which are ligated together, and an amplification primer which contains a restriction site. (Claim 44). You also teaches a second SDA primer. (Col. 3 line 15) (Claim 45). You also teaches a plurality of targets amplified in the same mixture, because multiple targets exist in the sample (Claims 56, 58-59). You also teaches detection of the target using fluorescent detection and a labeled probe. You also teaches denaturing double stranded nucleic acids (Col. 10), (Claims 61-66).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 46-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. as applied to claims 44-45 above, and further in view of Rothberg et al. (USPN 6,274,320.)

As disclosed above, You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55).

You et al. does not teach that the primer is attached to a substrate through biotin/streptavidin, or through a covalent bond.

Rothberg et al. teaches linking of anchor primers to a solid support. "In general, any nucleic acid capable of base-pairing can be used as an anchor primer. In some embodiments, the anchor primer is an oligonucleotide... The biotin-(strept-)avidin methodology provides several different ways to immobilize the anchor on the solid support." (Cols. 6-7). Rothberg also teaches that the primers may be linked via covalent bonds. (Col. 7, line 42).

It would have been obvious to combine the teachings of You and Rothberg. Even though Rothberg does not teach that the anchored primers of their invention are used for SDA, it would have been obvious to use them for any amplification reaction.

Using anchored primers would have allowed for easy detection of hybridized target, and for the use of different primers in different areas. This would have allowed for the identification of SNPs, and isolating specific mutant clones. It would have allowed for simultaneous sequencing and detection.

11. Claims 55 and 74-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. as applied to claim 44 above, and further in view of Walker et al. (Proc. Nat'l. Acad. Sci., Vol. 89, pages 392-396, 1992).

As disclosed above, You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55).

You does not teach modifying the primer or the amplicon.

Walker teaches the fundamental reaction scheme of SDA. They also teach modifying the primer by using a phosphorothioate linkage. "Extension of nonspecific complexes can be further reduced by using SDA primers whose 3' hydroxyl groups are modified to prevent extension by DNA polymerase." (Fig. 1, and page 394, bottom of second column.)

It would have been obvious to combine the teachings of You and Walker. This is because it would have been obvious to use a modified primer, as it would have been

incorporated in the amplicon and would have prevented extension of nonspecific complexes by DNA polymerase.

12. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. as applied to claim 56 above, and further in view of Walker et al. (USPN 5,624,825).

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55).

You does not teach the use of a universal primer.

Walker teaches the use of a universal primer in SDA. (Col. 8, lines 39-40).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of You with those of Walker. This is because using a universal primer would have allowed for amplification to occur even if the target were unknown. In other words, using a universal primer would have allowed for the target to be amplified regardless of whether the practitioner knew the sequence. This would have allowed for amplification of unknown sequences, which would have led to their identification, and would have been helpful in discovering sequences.

13. Claims 67, 69, and 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over You et al as applied to claim 61 above, and further in view of Lizardi et al (USPN 6,124,120).

As disclosed above, You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55).

You does not teach the incorporation of a labeled nucleotide into an amplicon or simultaneous amplification and detection.

Lizardi teaches multiple displacement amplification, which is based on SDA. "To aid in detection and quantification of nucleic acids amplified during the disclosed method, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules." (Col. 12, lines 20-24). (Claim 69). Lizardi also teaches the simultaneous amplification and detection of a target. (Col. 3, lines 49-66). (Claims 67 and 70).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You with those of Lizardi. First of all, it would have been obvious to incorporate detection labels directly into the amplicon. This would have allowed for rapid and precise identification of the amplified nucleic acid. It would have also been obvious to simultaneously amplify and detect the target, as this would have been more time efficient and would have allowed for the same detection conditions as amplification conditions, which would have allowed for more accurate results.

14. Claims 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. as applied to claim 44 above, and further in view of Stratagene Catalog, 1995.

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55).

You et al does not teach those specific restriction endonuclease sites recited in the claims.

Stratagene teaches multiple restriction endonucleases and their corresponding sites, including BstNI, HincII and HindIII. (page 235).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the restriction endonuclease recognition sequences found in the instant claims. This is because they were well known restriction sites and the corresponding endonucleases were readily available and were known to be useful in restricting nucleic acids.

15. Claims 120-124, 126, 128-132, 134-135, 142-159, 170, 175, and 198-203 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Lizardi and further in view of Heller (USPN 6,017,696).

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target

sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55). Therefore, You et al teaches two adjacent oligonucleotides which are ligated together, and an amplification primer which contains a restriction site. You also teaches a second SDA primer. (Col. 3 line 15). You also teaches a plurality of targets amplified in the same mixture, because multiple targets exist in the sample. You also teaches detection of the target using fluorescent detection and a labeled probe. You also teaches denaturing double stranded nucleic acids (Col. 10), (Claims 61-66).

You et al. does not teach using an electronically addressable microchip. You also does not teach simultaneous amplification and detection, or incorporation of a label into the amplicon.

Lizardi teaches multiple displacement amplification, which is based on SDA. Lizardi teaches "an address probe is an oligonucleotide having a sequence complementary to address tags on primers. The complementary portion of an address probe can be any length that supports specific and stable hybridization between the address probe and the address tag." (Col. 13, 60-65). Lizardi also teaches "To aid in detection and quantification of nucleic acids amplified during the disclosed method, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules." (Col. 12, lines 20-24). Lizardi also teaches the simultaneous amplification and detection of a target. (Col. 3, lines 49-66). Lizardi also teaches a washing step (Col. 14, line 65) (Claim 134).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You with those of Lizardi. First of all, it would have been obvious to incorporate detection labels directly into the amplicon. This would have allowed for rapid and precise identification of the amplified nucleic acid. It would have also been obvious to simultaneously amplify and detect the target, as this would have been more time efficient and would have allowed for the same detection conditions as amplification conditions, which would have allowed for more accurate results. Also, using a solid support would have allowed for easy detection of hybridized target, and for the use of different probes in different areas. This would have allowed for the identification of SNPs, and isolating specific mutant clones. It would have allowed for simultaneous sequencing and detection.

Neither You nor Lizardi teach that the array is electronically addressed.

Heller et al. teaches "A self-addressable, self-assembling microelectronic device is designed and fabricated to actively carry out and control multi-step and multiplex molecular biological reactions in microscopic formats. These reactions include nucleic acid hybridizations, antibody/antigen reactions, diagnostics, and biopolymer synthesis. The device can be fabricated using both microlithographic and micro-machining techniques. The device can electronically control the transport and attachment of specific binding entities to specific micro-locations. The specific binding entities include molecular biological molecules such as nucleic acids and polypeptides. The device can subsequently control the transport and reaction of analytes or reactants at the addressed specific micro-locations. The device is able to concentrate analytes and

reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be electronically replicated." (Abstract). Heller also teaches "By 'stringency control' is meant the ability to discriminate specific and non-specific binding interactions by changing some physical parameter. In the case of nucleic acid hybridizations, temperature control is often used for stringency. Reactions are carried out at or near the melting temperature (Tm) of the particular double-stranded hybrid pair." (Col. 6 bridging Col. 7), (Claim 135).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You and Lizardi with those of Heller. This is because, as Heller stated, using an electronic microarray would have been able to concentrate analytes and reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be also be electronically replicated. Furthermore, having the array be electronically based would have allowed for the signal to be imported into a computer program, which would have improved the processing and data handling.

16. Claims 125, and 172-175 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Lizardi in view of Heller, and further in view of Walker (PNAS article).

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized

to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55). Therefore, You et al teaches two adjacent oligonucleotides which are ligated together, and an amplification primer which contains a restriction site. You also teaches a second SDA primer. (Col. 3 line 15). You also teaches a plurality of targets amplified in the same mixture, because multiple targets exist in the sample. You also teaches detection of the target using fluorescent detection and a labeled probe. You also teaches denaturing double stranded nucleic acids (Col. 10), (Claims 61-66).

You et al. does not teach using an electronically addressable microchip. You also does not teach simultaneous amplification and detection, or incorporation of a label into the amplicon.

Lizardi teaches multiple displacement amplification, which is based on SDA. Lizardi teaches "an address probe is an oligonucleotide having a sequence complementary to address tags on primers. The complementary portion of an address probe can be any length that supports specific and stable hybridization between the address probe and the address tag." (Col. 13, 60-65). Lizardi also teaches "To aid in detection and quantification of nucleic acids amplified during the disclosed method, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules." (Col. 12, lines 20-24). Lizardi also teaches the simultaneous amplification and detection of a target. (Col. 3, lines 49-66). Lizardi also teaches a washing step (Col. 14, line 65) (Claim 134).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You with those of Lizardi. First of all, it would have been obvious to incorporate detection labels directly into the amplicon. This would have allowed for rapid and precise identification of the amplified nucleic acid. It would have also been obvious to simultaneously amplify and detect the target, as this would have been more time efficient and would have allowed for the same detection conditions as amplification conditions, which would have allowed for more accurate results. Also, using a solid support would have allowed for easy detection of hybridized target, and for the use of different probes in different areas. This would have allowed for the identification of SNPs, and isolating specific mutant clones. It would have allowed for simultaneous sequencing and detection.

Neither You nor Lizardi teach that the array is electronically addressed.

Heller et al. teaches "A self-addressable, self-assembling microelectronic device is designed and fabricated to actively carry out and control multi-step and multiplex molecular biological reactions in microscopic formats. These reactions include nucleic acid hybridizations, antibody/antigen reactions, diagnostics, and biopolymer synthesis. The device can be fabricated using both microlithographic and micro-machining techniques. The device can electronically control the transport and attachment of specific binding entities to specific micro-locations. The specific binding entities include molecular biological molecules such as nucleic acids and polypeptides. The device can subsequently control the transport and reaction of analytes or reactants at the addressed specific micro-locations. The device is able to concentrate analytes and

reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be electronically replicated." (Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You and Lizardi with those of Heller. This is because, as Heller stated, using an electronic microarray would have been able to concentrate analytes and reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be also be electronically replicated. Furthermore, having the array be electronically based would have allowed for the signal to be imported into a computer program, which would have improved the processing and data handling.

Neither You, Lizardi, or Heller teach modifying the primer or the amplicon.

Walker teaches the fundamental reaction scheme of SDA. They also teach modifying the primer by using a phosphorothioate linkage. "Extension of nonspecific complexes can be further reduced by using SDA primers whose 3' hydroxyl groups are modified to prevent extension by DNA polymerase." (Fig. 1, and page 394, bottom of second column.)

It would have been obvious to combine the teachings of You, Lizardi, and Heller with those of Walker. This is because it would have been obvious to use a modified primer, as it would have been incorporated in the amplicon and would have prevented extension of nonspecific complexes by DNA polymerase.

17. Claim 127 is rejected under 35 U.S.C. 103(a) as being unpatentable over You in view of Lizardi in view of Heller as applied to claim 126 above, and further in view of Walker et al. ('825).

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55). Therefore, You et al teaches two adjacent oligonucleotides which are ligated together, and an amplification primer which contains a restriction site. You also teaches a second SDA primer. (Col. 3 line 15). You also teaches a plurality of targets amplified in the same mixture, because multiple targets exist in the sample. You also teaches detection of the target using fluorescent detection and a labeled probe. You also teaches denaturing double stranded nucleic acids (Col. 10), (Claims 61-66).

You et al. does not teach using an electronically addressable microchip. You also does not teach simultaneous amplification and detection, or incorporation of a label into the amplicon.

Lizardi teaches multiple displacement amplification, which is based on SDA. Lizardi teaches "an address probe is an oligonucleotide having a sequence complementary to address tags on primers. The complementary portion of an address probe can be any length that supports specific and stable hybridization between the address probe and the address tag." (Col. 13, 60-65). Lizardi also teaches "To aid in

detection and quantification of nucleic acids amplified during the disclosed method, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules." (Col. 12, lines 20-24). Lizardi also teaches the simultaneous amplification and detection of a target. (Col. 3, lines 49-66). Lizardi also teaches a washing step (Col. 14, line 65) (Claim 134).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You with those of Lizardi. First of all, it would have been obvious to incorporate detection labels directly into the amplicon. This would have allowed for rapid and precise identification of the amplified nucleic acid. It would have also been obvious to simultaneously amplify and detect the target, as this would have been more time efficient and would have allowed for the same detection conditions as amplification conditions, which would have allowed for more accurate results. Also, using a solid support would have allowed for easy detection of hybridized target, and for the use of different probes in different areas. This would have allowed for the identification of SNPs, and isolating specific mutant clones. It would have allowed for simultaneous sequencing and detection.

Neither You nor Lizardi teach that the array is electronically addressed.

Heller et al. teaches "A self-addressable, self-assembling microelectronic device is designed and fabricated to actively carry out and control multi-step and multiplex molecular biological reactions in microscopic formats. These reactions include nucleic acid hybridizations, antibody/antigen reactions, diagnostics, and biopolymer synthesis. The device can be fabricated using both microlithographic and micro-machining

techniques. The device can electronically control the transport and attachment of specific binding entities to specific micro-locations. The specific binding entities include molecular biological molecules such as nucleic acids and polypeptides. The device can subsequently control the transport and reaction of analytes or reactants at the addressed specific micro-locations. The device is able to concentrate analytes and reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be electronically replicated." (Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You and Lizardi with those of Heller. This is because, as Heller stated, using an electronic microarray would have been able to concentrate analytes and reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be also be electronically replicated. Furthermore, having the array be electronically based would have allowed for the signal to be imported into a computer program, which would have improved the processing and data handling.

Neither You, Lizardi, or Heller teach the use of a universal primer.

Walker teaches the use of a universal primer in SDA. (Col. 8, lines 39-40).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of You, Lizardi, and Heller with those of Walker. This is because using a universal primer would have allowed for amplification to occur even if the target were unknown. In other words, using a universal primer would have

allowed for the target to be amplified regardless of whether the practitioner knew the sequence. This would have allowed for amplification of unknown sequences, which would have led to their identification, and would have been helpful in discovering sequences.

18. Claims 169-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over You in view of Lizardi in view of Heller as applied to claim 120 above, and further in view of Stratagene Catalog.

You et al. teaches "an amplification primer is an oligonucleotide for amplification of a target sequence by extension of the oligonucleotide after hybridization to the target sequence of by ligation of multiple oligonucleotides which are adjacent when hybridized to the target sequence...The SDA amplification primer further comprises a recognition site for restriction endonuclease 5' to the target binding sequence." (Col. 2, lines 40-55). Therefore, You et al teaches two adjacent oligonucleotides which are ligated together, and an amplification primer which contains a restriction site. You also teaches a second SDA primer. (Col. 3 line 15). You also teaches a plurality of targets amplified in the same mixture, because multiple targets exist in the sample. You also teaches detection of the target using fluorescent detection and a labeled probe. You also teaches denaturing double stranded nucleic acids (Col. 10), (Claims 61-66).

You et al. does not teach using an electronically addressable microchip. You also does not teach simultaneous amplification and detection, or incorporation of a label into the amplicon.

Lizardi teaches multiple displacement amplification, which is based on SDA. Lizardi teaches "an address probe is an oligonucleotide having a sequence complementary to address tags on primers. The complementary portion of an address probe can be any length that supports specific and stable hybridization between the address probe and the address tag." (Col. 13, 60-65). Lizardi also teaches "To aid in detection and quantification of nucleic acids amplified during the disclosed method, detection labels can be directly incorporated into amplified nucleic acids or can be coupled to detection molecules." (Col. 12, lines 20-24). Lizardi also teaches the simultaneous amplification and detection of a target. (Col. 3, lines 49-66). Lizardi also teaches a washing step (Col. 14, line 65) (Claim 134).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You with those of Lizardi. First of all, it would have been obvious to incorporate detection labels directly into the amplicon. This would have allowed for rapid and precise identification of the amplified nucleic acid. It would have also been obvious to simultaneously amplify and detect the target, as this would have been more time efficient and would have allowed for the same detection conditions as amplification conditions, which would have allowed for more accurate results. Also, using a solid support would have allowed for easy detection of hybridized target, and for the use of different probes in different areas. This would have allowed for the identification of SNPs, and isolating specific mutant clones. It would have allowed for simultaneous sequencing and detection.

Neither You nor Lizardi teach that the array is electronically addressed.

Heller et al. teaches "A self-addressable, self-assembling microelectronic device is designed and fabricated to actively carry out and control multi-step and multiplex molecular biological reactions in microscopic formats. These reactions include nucleic acid hybridizations, antibody/antigen reactions, diagnostics, and biopolymer synthesis. The device can be fabricated using both microlithographic and micro-machining techniques. The device can electronically control the transport and attachment of specific binding entities to specific micro-locations. The specific binding entities include molecular biological molecules such as nucleic acids and polypeptides. The device can subsequently control the transport and reaction of analytes or reactants at the addressed specific micro-locations. The device is able to concentrate analytes and reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be electronically replicated." (Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of You and Lizardi with those of Heller. This is because, as Heller stated, using an electronic microarray would have been able to concentrate analytes and reactants, remove non-specifically bound molecules, provide stringency control for DNA hybridization reactions, and improve the detection of analytes. The device can be also be electronically replicated. Furthermore, having the array be electronically based would have allowed for the signal to be imported into a computer program, which would have improved the processing and data handling.

Neither You, Lizardi, nor Heller teach those specific restriction endonucleases found in the claims.

Stratagene teaches multiple restriction endonucleases and their corresponding sites, including BstNI, HincII, BstXI, and HindIII. (page 235).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the restriction endonuclease recognition sequences found in the instant claims. This is because they were well known restriction sites and the corresponding endonucleases were readily available and were known to be useful in restricting nucleic acids.

Summary

19. Claims 66, 71, 134, 154, and 169 is rejected under 35 U.S.C. 112, second paragraph. Claims 44-210 are rejected under the judicially created doctrine of obviousness-type double patenting. Claims 44-45, 56, 58-59, 61-66 and 68 are rejected under 35 U.S.C. 102(e) as being anticipated by You et al. Claims 46-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Rothberg et al. Claims 55 and 74-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Walker et al. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Walker et al. Claims 67, 69, and 70 is rejected under 35 U.S.C. 103(a) as being unpatentable over You et al in view of Lizardi et al. Claims 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Stratagene Catalog, 1995. Claims 120-124, 126, 128-132, 134-135, 142-159, 175, and 198-203 are rejected under 35 U.S.C. 103(a) as being unpatentable over You

et al. in view of Lizardi and further in view of Heller. Claims 125, and 172-175 are rejected under 35 U.S.C. 103(a) as being unpatentable over You et al. in view of Lizardi in view of Heller, and further in view of Walker. Claim 127 is rejected under 35 U.S.C. 103(a) as being unpatentable over You in view of Lizardi in view of Heller as applied to claim 126 above, and further in view of Walker et al. Claims 169-171 are rejected under 35 U.S.C. 103(a) as being unpatentable over You in view of Lizardi in view of Heller as applied to claim 120 above, and further in view of Stratagene Catalog. The following claims are free of the prior art but are rejected for other reasons (i.e., double patenting rejection): 60, 78--119, 133, 136-141, 160-168, 176-197, and 204-210.

Conclusion

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or

872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

April 17, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600